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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/723,326	11/28/2000	Keith A. Webster	10989-004-999	5537

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EXAMINER	
MCKELVEY, TERRY ALAN	
ART UNIT	**PAPER NUMBER**
1636	29

DATE MAILED: 11/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/723,326	WEBSTER, KEITH A.	
	Examiner	Art Unit	
	Terry A. McKelvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27 and 42-60* is/are pending in the application.

4a) Of the above claim(s) *2,3,10,13-17,20,54,55 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-9,11,12,18,19,21-27,42-53,56-58 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/28/00* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7, 17* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, species: cardiac muscle-specific promoter, HRE element from the erythropoietin gene, VEGF nucleotide sequence, and human synapsin silencer, claims 1, 4-9, 11, 12, 18, 19, 21-27, 42-53, 56-58, and 60 in Paper Nos. 16, filed 9/5/02, and 24, filed 5/12/03 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 2-3, 10, 13-17, 20, 54-55, and 59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper Nos. 16 and 24.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-6, 11-12, 19, 21, 23-24, 26-27, 42, and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by Webster et al (WO 96/20276).

Webster et al teach expression vectors comprising a hypoxia response element (HRE) from the erythropoietin gene (reads on SEQ ID NO:1) operatively linked to a tissue-specific promoter, such as a cardiac-specific promoter (pages 5-6 and 12). It is taught that the expression vector may be a plasmid, a replication-defective adenovirus vector, retrovirus vector, or the like (pages 6 and 33). Termination, polyadenylation, and other sequences for effective expression in cells may be in the expression vectors (page 20). The expression vector containing a luciferase reporter gene is also taught (pages 32 and 44). This reference also teaches that: "A further desirable characteristic of promoters useful in the present invention is that they possess a relatively low activity in the absence of activated hypoxia-regulated enhancer elements, even in the target tissues. One means of achieving this is to select promoters of genes encoding proteins that have a relatively low turnover rate in adult tissue, such as the actin and alpha-MHC promoters described herein. Another means is to use "silencer"

elements, which suppress the activity of a selected promoter in the absence of hypoxia." (page 12). This reads on adding a heterologous silencer element to the constructs taught by the reference in order to reduce expression from the promoter in the absence of the induction by hypoxia (i.e., forming a silencer-inducible region as claimed).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-9, 11-12, 18-19, 21-27, 42-53, 56-58, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webster et al (WO 96/20276) in view of Li et al (applicant reference KR).

Webster et al teach expression vectors comprising a hypoxia response element (HRE) from the erythropoietin gene (reads on SEQ ID NO:1) operatively linked to a tissue-specific promoter, such as a cardiac-specific promoter (pages 5-6 and 12). It is

taught that the expression vector may be a plasmid, a replication-defective adenovirus vector, retrovirus vector, or the like (pages 6 and 33). Termination, polyadenylation, and other sequences for effective expression in cells may be in the expression vectors (page 20). The expression vector containing a luciferase reporter gene is also taught (pages 20, 32, and 44). This reference also teaches that: "A further desirable characteristic of promoters useful in the present invention is that they possess a relatively low activity in the absence of activated hypoxia-regulated enhancer elements, even in the target tissues. One means of achieving this is to select promoters of genes encoding proteins that have a relatively low turnover rate in adult tissue, such as the actin and alpha-MHC promoters described herein. Another means is to use "silencer" elements, which suppress the activity of a selected promoter in the absence of hypoxia." (page 12). This reads on adding a heterologous silencer element to the constructs taught by the reference in order to reduce expression from the promoter in the absence of the induction by hypoxia (i.e., forming a silencer-inducible region as claimed).

Webster et al do not specifically teach the expression of VEGF in the expression vectors, use of the silencer from the human synapsin gene in the expression vectors, that the silencer

overlaps the HRE element, is within 50, 100, 200, or 500 bp of the HRE element, the HRE and silencer elements are duplicated and arranged in alternating patterns, the silencer element is in the antisense or sense orientation with respect to the nucleotide sequence (of the heterologous gene), and that the expression vector comprises polylinker restriction sites.

Li et al teach a silencer element from the human synapsin gene which is capable of conferring repression on a heterologous promoter in nonneuronal cells (abstract). This silencer comprises a neuron restrictive silencer element to which neuron restrictive silencer binds.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the silencer from the human synapsin gene taught by Li et al in the expression vectors containing HRE, a cardiac muscle-specific promoter, and a heterologous gene, and a silencer which suppresses activity from the promoter in the absence of hypoxia taught by Webster et al because Li et al teach that it is within the ordinary skill in the art to use the silencer from the human synapsin gene to confer repression on a heterologous promoter in nonneuronal cells and Webster et al teach that it is within the ordinary skill in the art to use a silencer in the expression vectors

they teach, which silencer is able to reduce expression from the promoter in the absence of hypoxia.

One would have been motivated to do so for the expected benefit of using a silencer that is known in the art to be functional with heterologous promoters in nonneuronal cells as taught by Li et al, in the expression vectors taught by Webster et al as being desirable to have low activity from the promoter when uninduced, specifically by use of a silencer element.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Regarding the expression of the coding region of VEGF in the vectors, it would have been obvious to express any therapeutic or deleterious gene, including VEGF (in either the sense or antisense orientation) in the expression vectors made from the combined teachings of the cited references because Webster et al teach that various therapeutic and deleterious genes can be expressed by the hypoxia controlled vectors taught by the reference and VEGF is and was well known hypoxia-associated gene that, depending on the context, can be either therapeutic or deleterious and thus expression in either the

sense (to increase VEGF) or antisense (to decrease VEGF) as desired would have been obvious.

Regarding the use of different distances between the silencer and HRE, duplication of the two elements and arrangement in alternating patterns, and the orientation of the silencer versus the promoter, it would have been obvious to use any of the indicated distances or arrangements because it is and was well known and well within the ordinary skill in the art to use any distance for spacing of silencers versus the other elements because within the art it is known that there is great flexibility in spacing of such elements because silencers can act over short and long distances, including overlapping, 50 bp, up to 500 bp, or more, and that either sense orientation is permissible with respect with the promoter because silencers are by definition orientation independent. Furthermore, it would have been obvious to duplicate the elements and alternate them because use of duplicated silencer and inducible elements is and was well known in the art, including various ways of orienting them.

Regarding the use of polylinker restriction sites, it is and was well known in the art to use such polylinkers in order to facilitate expression vector construction.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 50 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 49. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

In the instant case, claims 49 and 50 are identical in wording and thus are duplicates.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is 703-872-9306. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning rejections or other major issues in this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

November 3, 2003